FGFR2 Abnormalities Underlie a Spectrum of Bone, Skin, and Cancer Pathologies

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Fibroblast growth factor receptor (FGFR)2 is regulated on the basis of the balance of FGFs, heparan-sulfate proteoglycans, FGFR2 isoforms, endogenous inhibitors, and microRNAs. FGFR2 signals cross-talk with hedgehog, bone morphogenetic protein, and other regulatory networks. Some cases of congenital skeletal disorders with an *FGFR2* mutation show skin phenotypes, including acne, cutis gyrata, and acanthosis nigricans. Gain-of-function mutations or variations of human *FGFR2* occur in estrogen receptor-positive breast cancer, diffuse-type gastric cancer, and endometrial uterine cancer. Oral administration of AZD2171 or Ki23057 inhibits *in vivo* proliferation of cancer cells with aberrant FGFR2 activation in rodent therapeutic models. However, loss-of-function mutations of *FGFR2* are reported in human melanoma. Conditional *Fgfr2b* knockout in the rodent epidermis leads to increased macrophage infiltration to the dermis and adipose tissue, epidermal thickening accompanied by basal-layer dysplasia and parakeratosis, and the promotion of chemically induced squamous-cell carcinoma. Dysregulation of FGFR2 results in a spectrum of bone and skin pathologies and several types of cancer.

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INTRODUCTION

FGFR1, *FGFR2*, *FGFR3*, and *FGFR4* genes encode receptors for fibroblast growth factors (FGFs) that are involved in fetal morphogenesis, adult tissue homeostasis, and tumorigenesis (Dailey *et al.*, 2005; Eswarakumar *et al.*, 2005; Grose and Dickson, 2005; Wilkie, 2005; Chaffer *et al.*, 2007). The *BAG4–PPAPDC1B–FGFR1–TACC1* locus at human chromosome 8p11–p12 and the *BAG3–PPAPDC1A–FGFR2–TACC2* locus at human chromosome 10q26.12–q26.13 are syntenic blocks generated by ancient whole-genome duplications during vertebrate evolution (Katoh and Katoh, 2003b; Itoh and Ornitz, 2004). *FGFR1* and *FGFR2* are paralogs in the *FGFR* gene family.

The *FGFR2* gene encodes several splice variants by alternative splicing (Dionne *et al.*, 1990; Miki *et al.*, 1991; Savagner *et al.*, 1994; Katoh and Katoh, 2003a). Fibroblast growth factor receptor (FGFR)2b and FGFR2c are representative FGFR2 isoforms among several splice variants derived from the *FGFR2* gene. FGFR2b, in epithelial cells, and FGFR2c, in mesenchymal cells, are almost identical transmembrane-type receptors with extracellular immunoglobulin-like domains and cytoplasmic tyrosine-kinase domain. FGFR2b functions as the receptor for FGF1, FGF3, FGF7, FGF10, and FGF22, whereas FGFR2c functions as the receptor for FGF1, FGF2, FGF4, FGF6, FGF9, FGF16, FGF17, FGF18, and FGF20 (Ornitz *et al.*, 1996; Eswarakumar *et al.*, 2005; Zhang *et al.*, 2006). As the latter half of the third immunoglobulin-like domain of FGFR2b and FGFR2c is completely different because of alternative splicing of mutually exclusive exons, FGFR2b and FGFR2c show distinct ligand specificity.

Heparan-sulfate proteoglycan is a scaffolding protein that mediates the interaction of FGFs and FGFR2 in a tissue-specific manner (Mohammadi *et al.*, 2005; Luo *et al.*, 2006). FGFs that are associated with heparan sulfate proteoglycan induce dimerization and autophosphorylation of FGFR2 on Y657 in the activation loop of the tyrosine kinase domain to release FGFR2 from autoinhibition (Dailey *et al.*, 2005; Eswarakumar *et al.*, 2005; Chen *et al.*, 2007). FGFR2 then phosphorylates fibroblast growth factor receptor substrate (FRS)2/FRS2α/Sucl-associated neurotrophic factor target 1 (Wang *et al.*, 1996; Hadari *et al.*, 2001) to recruit growth factor receptor-bound protein 2 for the activation of the SOS—Ras–Raf—MEK(MAPK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) kinase)–ERK (extracellular signal-regulated kinase) or the Gab1–phosphoinositide-3 kinase –Akt signaling cascade. Activated FGFR2 directly recruits phospholipase *C*-γ to catalyze phosphatidylinositol diphosphate to inositol triphosphate and diacylglycerol. Inositol triphosphate induces Ca^{2+} release from the endoplasmic reticulum,

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Abbreviations: BCC, basal cell carcinoma; ER, estrogen receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; miRNA, microRNA; SCC, squamous cell carcinoma; SNP, single nucleotide polymorphism

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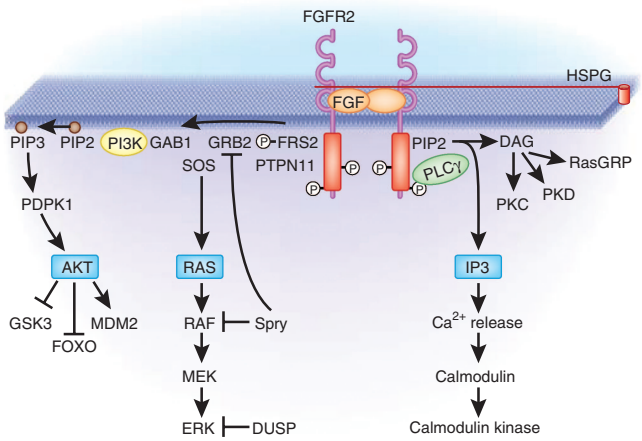

Figure 1. FGFR2 signaling cascades. Fibroblast growth factor receptor (FGFR)2b functions as a receptor for fibroblast growth factor (FGF)1, FGF3, FGF7, FGF10 and FGF22, whereas FGFR2c functions as a receptor for FGF1, FGF2, FGF4, FGF6, FGF9, FGF16, FGF17, FGF18 and FGF20. FGFR2 transduces FGF signals to Ras-extracellular signal-regulated kinase(ERK), phosphoinositide-3 kinase (PI3K)-Akt, Ca^{2+}, and diacylglycerol (DAG) signaling cascades. The FGF–ERK signaling cascade is involved in cell proliferation. The FGF–PI3K signaling cascade is involved in cell survival and polarity control. Sprouty inhibits the FGF–ERK signaling cascade at growth factor receptor-bound protein 2 and Raf, whereas dual-specificity phosphatase inhibits the FGF–ERK signaling cascade at ERK. FGFR2 is regulated on the basis of the balance of FGFs, heparan-sulfate proteoglycan (HSPG), FGFR2 isoforms, and endogenous inhibitors.

whereas diacylglycerol activates protein kinase C, protein kinase D, or RasGRP (guanyl nucleotide-releasing protein) signaling cascades. FGFR2 transduces FGF signals to Ras-extracellular signal-regulated kinase, phosphoinositide-3 kinase-Akt, Ca^{2+}, and diacylglycerol signaling cascades (Figure 1).

FGFR2 is regulated on the basis of the balance of FGFs, heparan-sulfate proteoglycans, FGFR2 isoforms, and endogenous inhibitors (Figure 1). Sprouty inhibits the FGF-extracellular signal-regulated kinase signaling cascade at growth factor receptor-bound protein 2 and Raf, whereas dual-specificity phosphatase inhibits the FGF-extracellular signal-regulated kinase signaling cascade at extracellular signal-regulated kinase. microRNAs (miRNAs) are emerging as crucial regulators of various signaling networks (Bartel, 2004; Negrini *et al.*, 2007; Grosshans and Filipowicz, 2008; Katoh and Katoh, 2008). MiR-433 represses translation of FGF20 in individuals with the *C* allele of the rs12720208 single nucleotide polymorphism (SNP) (Wang *et al.*, 2008), whereas miR-21 represses translation of functions of FGFR signaling inhibitor, Spry1 (Thum *et al.*, 2008).

Germline Fgfr2b-knockout mice die shortly after birth because of multiple-organ abnormalities, such as agenesis of the lungs, limbs, anterior pituitary gland, and thyroid gland and dysgenesis of the skin, glandular stomach, pancreas, and thymus (De Moerlooze *et al.*, 2000; Revest *et al.*, 2001). Genetic alterations of *FGFR2* at germline or somatic level gives rise to congenital disorders and acquired diseases through dysregulation of FGFR2 signaling cascades (Grose and Dickson, 2005; Wilkie, 2005; Katoh, 2008). Genome-wide association studies are opening up new opportunities for research on FGFR2-associated diseases (Easton *et al.*, 2007; Hunter *et al.*, 2007). Here, FGFR2-associated disorders or diseases are summarized in Table 1, and then skin manifestations caused by *FGFR2* genetic alterations are reviewed. As melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are representative skin malignancies, perspectives on these malignancies are also described with an emphasis on *FGFR2* genetics.

HUMAN DISORDERS OR DISEASES ASSOCIATED WITH *FGFR2*

Congenital skeletal disorders

FGFR2c is expressed on mesenchymal cells during the early phase of long-bone formation, known as the mesenchymal condensation process. FGFR2 is also expressed on preosteoblasts and osteoblasts during the later phase of bone formation (Eswarakumar *et al.*, 2002). The nuclear factor-Y transcription factor binds to the evolutionarily conserved CCAAT motif in the proximal promoter region of *FGFR2* gene, and is involved in basal expression of *FGFR2* (Sun *et al.*, 2009). Bone morphogenetic protein 2 induces FGFR2 upregulation in C3H10T1/2 embryonic-fibroblast cells; however, the mechanism of the FGFR2 induction by bone morphogenetic protein-Smad signaling remains unclear. As FGFR2 is involved in bone formation, *FGFR2* is a causative gene for several congenital skeletal disorders manifested by short-limbed bone dysplasia or craniosynostosis (Passos-Bueno *et al.*, 1999; Kan *et al.*, 2002; Wilkie, 2005).

The *FGFR2* gene is mutated in Crouzon syndrome (Reardon *et al.*, 1994), Jackson–Weiss syndrome (Jabs *et al.*, 1994), Apert syndrome (Wilkie *et al.*, 1995), Pfeiffer syndrome (Rutland *et al.*, 1995), Beare–Stevenson syndrome (Przylepa *et al.*, 1996), and Saethre–Chotzen syndrome (Paznekas *et al.*, 1998). Missense mutations of FGFR2 in congenital skeletal disorders are clustered around the third immunoglobulin-like domain or within the tyrosine kinase domain (Figure 2). Amino-acid substitutions around the third immunoglobulin-like domain induce autocrine FGFR2 activation through altered FGF-binding specificity (Yu *et al.*, 2000), whereas those in the tyrosine kinase domain induce ligand-independent FGFR2 activation by the releasing FGFR2 from autoinhibition (Chen *et al.*, 2007).

Breast cancer

Gene amplification of the *FGFR2* gene occurs in primary breast cancer (Adnane *et al.*, 1991). *FGFR2* gene amplification results in overexpression of the *FGFR2* gene products, especially C-terminally truncated FGFR2 protein, because of the exclusion of the last exon from the amplicon during the gene amplification process (Katoh and Katoh, 2003a). C-terminally truncated FGFR2 induces constitutive activation of FGFR2 signaling cascades in a

Table 1. Genetic variations and alterations of *FGFR2*

Disease	Germ or soma	Genetic alteration or variation	Reference
Cancer			
Breast cancer	Somatic	Copy-number gain	Adnane *et al.* (1991)
	Somatic	Missense mutation	Stephens *et al.* (2005)
	Germ-line	Intronic regulatory SNPs	Easton *et al.* (2007)
Gastric cancer	Somatic	Copy-number gain	Nakatani *et al.* (1990)
	Somatic	Missense mutation	Jang *et al.* (2001)
Endometrial uterus cancer	Somatic	Missense mutation	Pollock *et al.* (2007)
Lung cancer	Somatic	Missense mutation	Davies *et al.* (2005)
Melanoma	Somatic	Missense mutation	Gartside *et al.* (2009)
Non-cancerous disease			
Crouzon syndrome	Germ-line	Missense mutation	Reardon *et al.* (1994)
Jackson–Weiss syndrome	Germ-line	Missense mutation	Jabs *et al.* (1994)
Apert syndrome	Germ-line	Missense mutation	Wilkie *et al.* (1995)
Pfeiffer syndrome	Germ-line	Missense mutation	Rutland *et al.* (1995)
Beare–Stevenson syndrome	Germ-line	Missense mutation	Przylepa *et al.* (1996)
Saethre–Chotzen syndrome	Germ-line	Missense mutation	Paznekas *et al.* (1998)
Atopic dermatitis	Germ-line	Intronic marker SNPs	Park *et al.* (2008)

FGFR2, fibroblast growth factor receptor 2; SNPs, single-nucleotide polymorphisms.

ligand-independent manner (Moffa and Ethier, 2007). R203C missense mutation of the *FGFR2* gene also occurs in primary breast cancer (Stephens *et al.*, 2005). FGFR2 signaling is aberrantly activated in breast cancer through genetic alterations of *FGFR2*.

Genome-wide association studies and candidate-approach association studies showed that rs35054928, rs2981578, rs2912778, rs2912781, rs35393331, rs10736303, rs7895676, and rs33971856 SNPs in intron 2 of the *FGFR2* gene are associated with breast cancer (Easton *et al.*, 2007; Huijts *et al.*, 2007; Hunter *et al.*, 2007; Meyer *et al.*, 2008; Stacey *et al.*, 2008). A putative estrogen receptor (ER)-binding site is created on the risk allele of rs10736303 (Easton *et al.*, 2007). *FGFR2* is preferentially upregulated in ER-positive primary breast cancer (Tozlu *et al.*, 2006), and the *FGFR2* risk allele is associated with ER-positive breast cancer (Stacey *et al.*, 2008).

Gastric cancer

Gastric cancer is classified into the intestinal type and the diffuse type (Lauren, 1965). The *ERBB2* gene is preferentially amplified in the intestinal-type gastric cancer, frequently associated with liver metastasis, whereas the *FGFR2* gene is preferentially amplified in the diffuse-type gastric cancer, frequently associated with peritoneal dissemination. The two types of gastric cancer, with distinct clinicopathological features, show type-specific genetic alterations (Katoh and Terada, 1993; Katoh and Katoh, 2004).

FGFR2 signaling is aberrantly activated in diffuse-type gastric cancer because of gene amplification or missense mutations (Nakatani *et al.*, 1990; Jang *et al.*, 2001). Small-molecule FGFR inhibitor Ki23057 inhibits proliferation and peritoneal dissemination of gastric cancer cells with *FGFR2* gene amplification, mainly by inhibitory effects on the MAPK signaling cascade (Nakamura *et al.*, 2006). Small-molecule FGFR inhibitors PD173074 and AZD2171 also show similar effects (Mohammadi *et al.*, 1998; Wedge *et al.*, 2005).

The association between SNPs in intron 2 of the *FGFR2* gene and diffuse-type gastric cancer remains unknown. As diffuse-type gastric cancer is enriched in reproductive females, it is speculated that diffuse-type gastric cancer might be associated with ER signaling at least in reproductive females. Therefore, large-scale stratified analyses should be carried out on *FGFR2* SNPs and ER status in diffuse-type gastric cancer.

Endometrial uterine cancer

Missense mutations of the *FGFR2* gene also occur in endometrial uterine cancer, resulting in amino-acid substitutions around the third immunoglobulin-like domain (S252W, K310R, S373C, Y376C, C383R, M392R), and those in the tyrosine-kinase domain (I547V, N549K, K659E) (Pollock *et al.*, 2007). These FGFR2 mutations result in aberrant activation of FGFR2 signaling as mentioned above. The small-molecule FGFR inhibitor PD173074 inhibits proliferation and survival of endometrial uterine-cancer cells with *FGFR2* mutations (Dutt *et al.*, 2008).

The breast cancer risk allele of rs2981578 SNP in intron 2 of the *FGFR2* gene is associated with a decreased, rather than increased, risk of endometrial uterine cancer (McGrath *et al.*, 2008). As the uterus is an estrogen-responsive organ, large-scale stratified analyses should also be carried out on *FGFR2* SNPs and ER status in endometrial uterine cancer.

CUTANEOUS PHENOTYPES OF *FGFR2* ALTERATION OR VARIATION

Cutaneous FGFR2b

FGFR2b is expressed in epidermal keratinocytes, hair follicles, and sebaceous glands (Danilenko *et al.*, 1995; auf demKeller *et al.*, 2004). FGF7, FGF10, and FGF22 are FGFR2b ligands secreted by fibroblast, smooth muscle cells, endothelial cells, skin dermis, and γδT cells to induce proliferation and differentiation of epidermal keratinocytes (Finch *et al.*, 1989; Smola *et al.*, 1993; Boismenu and Havran, 1994; Winkles *et al.*, 1997; Marchese *et al.*, 2001). For example, FGF7 expression in mesenchymal cells is upregulated by platelet-derived growth factor derived from platelets and by IL-1, IL-1β and tumor necrosis factor-α derived from polymorphonuclear leukocytes or macrophages (Werner *et al.*, 1992; Brauchle *et al.*, 1994; Chedid *et al.*, 1994). FGFR2b ligands are

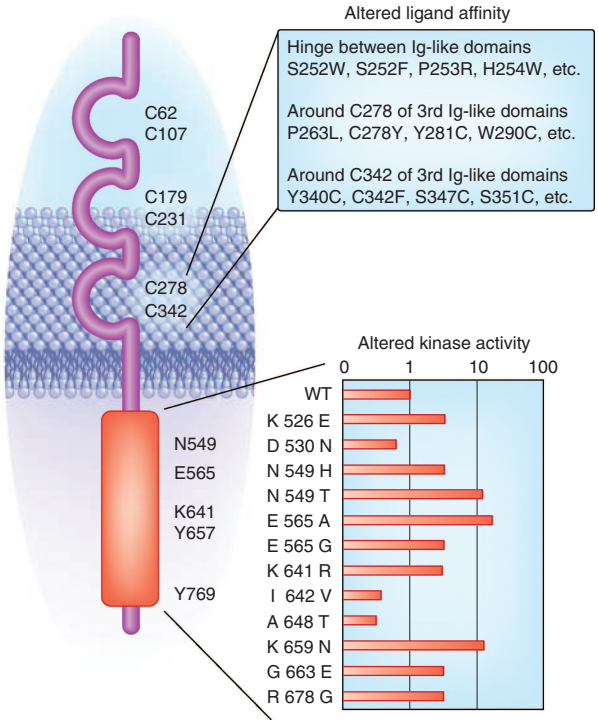

Figure 2. Domain architecture and mutations of FGFR2. Fibroblast growth factor receptor (FGFR)2b and FGFR2c are transmembrane-type receptors with extracellular immunoglobulin-like domains and cytoplasmic tyrosine-kinase domain. Wild-type FGFR2 kinase is autoinhibited in the absence of FGF signaling by the kinase hinge, constituted by N549, E565 and K641, and it is activated in the presence of FGF signaling by autophosphorylation of Y657 in the activation loop. Missense mutations around the third immunoglobulin-like domain results in altered ligand affinity. Some missense mutations in the kinase domain increase the kinase activity in congenital skeletal disorders and in endometrial cancer, whereas other missense mutations in the kinase domain decrease kinase activity at least *in vitro*.

upregulated in the skin by cytokines and growth factors during physiological and pathological processes (auf dem-Keller *et al.*, 2004).

Melanoma

Recently, missense mutations of FGFR2c around the third immunoglobulin-like domain or in the tyrosine-kinase domain were also reported in melanoma (Gartside *et al.*, 2009). FGFR2c mutations in melanoma around the third immunoglobulin-like domain are involved in altered ligand specificity, which is similar to congenital skeletal diseases and other types of cancer (Figure 2). FGFR2c mutations in melanoma in the tyrosine kinase domain, such as D530N, I642V, and A648T, are associated with decreased, rather than increased, kinase activity *in vitro*, but they are not associated with decreased tumorigenicity *in vivo* (Gartside *et al.*, 2009). The D530N mutation is predicted to affect the structure of the kinase hinge, whereas I642V and A648T mutations are predicted to affect the structure of the autophosphorylation loop (Figure 2).

Mouse cutaneous SCC

Epidermal growth and hair-follicle morphogenesis are severely hampered in the skin of the germline-Fgfr2b-knockout mice (Revest *et al.*, 2001; Petiot *et al.*, 2003). Conditional-knockout technology expressing Cre recombinase under the control of bovine keratin 5 promoter (Cre-K5) in FGFR2b$^{flox/flox}$ mice was then applied to elucidate the role of FGFR2b during skin homeostasis. Mice lacking FGFR2b in the skin epidermis manifest a thin and silky coat, sebaceous gland atrophy, increased macrophage infiltration to the dermis and the adipose tissue, and epidermal thickening accompanied by basal-layer dysplasia and parakeratosis (Grose *et al.*, 2007).

Conditional-FGFR2b knockout in the skin epidermis leads to an increased incidence of SCC in mice treated with 7,12-dimethylbenz[α]anthracene and 12-*O*-tetradecanoylphorbol-13-acetate (Grose *et al.*, 2007). Intraepithelial γδT cells are involved in the production of FGFR2 ligand during the wound-healing process, and mice lacking γδT cells also show an increased incidence of 7,12-dimethylbenz[α]anthracene/12-*O*-tetradecanoylphorbol-13-acetate-induced SCC (Girardi *et al.*, 2001). As FGFR2b is involved in the maintenance of cutaneous homeostasis and in wound healing, inactivation of FGFR2b results in enhanced sensitivity of the mouse skin to chemical carcinogenesis.

Acne

The *FGFR2* gene is mutated in Apert syndrome, as mentioned above (Wilkie *et al.*, 1995). Apert-syndrome patients with craniosynostosis show early onset of severe acne, spreading in an unusual pattern to the extensor aspects of the forearms (Solomon *et al.*, 1970). Epidermal *FGFR2* mutations because of genetic mosaicism also result in severe acne, which is characterized as unilateral acneiform nevus (Munro and Wilkie, 1998).

As androgen receptor (AR)-induced upregulation of FGF7 or FGF10 in skin mesenchymal cells results in FGFR2b activation in the sebaceous gland, FGFR2 is predicted to be involved in the pathogenesis of acne (Melnik and Schmitz, 2008).

Cutis gyrata and acanthosis nigricans

The *FGFR2* gene is mutated in Beare–Stevenson syndrome, as mentioned above (Przylepa *et al.*, 1996). Beare–Stevenson syndrome is featured by craniosynostosis and skin phenotypes, such as cutis gyrata and acanthosis nigricans (Hall *et al.*, 1992). Cutis gyrata is characterized by skin furrows of corrugated appearance, particularly on the face, near the ears, and sometimes on the palms and soles. Acanthosis nigricans is characterized by pigmented velvety areas on the hands, feet, or genital region. The mechanisms by which cutis gyrata and acanthosis nigricans are induced

by the *FGFR2* mutations remain unclear.

Atopic dermatitis

Atopic dermatitis is a chronic, relapsing, inflammatory skin disorder characterized by enhanced IgE responses to common environmental allergens (Cooper, 1994). Genetic predisposition and environmental insult result in altered epidermal structure and function, and the hyper-activated immune system then disrupts skin-barrier homeostasis (Elias and Steinhoff, 2008). On the basis of a candidate-approach association study using 525 cases of atopic dermatitis, it was recently claimed that a haplotype of SNPs in intron 17 of the *FGFR2* gene is associated with atopic dermatitis with a *P*-value of 0.01 (Park *et al.*, 2008). As the association is not strong, a large-scale confirmatory study is necessary to draw conclusions.

PERSPECTIVES ON THE DERMATOLOGICAL GENETICS OF *FGFR2*

Melanoma

FGFR2c mutations identified in melanoma are informative for understanding the regulatory mechanisms of FGFR2 kinase (Figure 2). However, as FGF2 signaling through FGFR1c plays a pivotal role in the proliferation and survival of melanoma cells (Halaban, 1996; Wang and Becker, 1997), loss-of-function mutations of FGFR2c in melanoma might be passenger mutations. Bi-allelic analyses of FGFR2c mutations or deletions in human melanoma, as well as *in vivo* analyses using conditional FGFR2-knockout and a mutant FGFR2c transgenic mouse model, are necessary to elucidate the biological role of FGFR2c mutations in melanoma.

Human cutaneous SCC

As mouse genetics indicates that FGFR2b functions as a tumor suppressor in the skin epidermis, as mentioned above, it is predicted that decreased FGFR2b signaling is favorable for the development of SCC in human skin. Breast cancer risk alleles of *FGFR2* SNPs might be inversely correlated with the risk of human cutaneous SCC. Alternatively, deletions or loss-of-function mutations of the *FGFR2* gene might occur in human cutaneous SCC. Therefore, genetic and genomic analyses of the *FGFR2* gene are necessary to clarify the association between FGFR2b inactivation and human cutaneous SCC.

BCC

BCC is one of most common malignancies among Caucasians (Bastiaens *et al.*, 1998). BCC occurs because of genetic predispositions and environmental insults by UV light. Nevoid basal cell carcinoma syndrome is characterized by cutaneous BCC, epidermal cysts, palmar pits, jaw keratocysts, calcified dural folds, skeletal anomalies, cleft lip, and other tumors such as medulloblastoma and meningioma (Gorlin, 1995). Loss-of-function mutations of the *patched*/*PTCH1* gene and gain-of-function mutations of the *smoothened*/*SMO* gene occur in nevoid basal cell carcinoma syndrome, as well as in sporadic BCC (Gailani *et al.*, 1996; Hahn *et al.*, 1996; Johnson *et al.*, 1996; Reifenberger *et al.*, 1998; Wicking *et al.*, 1999). Patched is a receptor for the hedgehog family members (Stone *et al.*, 1996), whereas smoothened is a signal transducer of the hedgehog signaling cascade (van den Heuvel and Ingham, 1996). Hedgehog signaling activation is the driving force of BCC (Epstein, 2008). As the FGF–FGFR2b signaling cascade cross-talks with the hedgehog signaling cascade (Bellusci *et al.*, 1997; Revest *et al.*, 2001; Spencer-Dene *et al.*, 2006), the combined effects of *FGFR2* SNPs and environmental factors in BCC should be further investigated in the future.

CONCLUDING REMARKS

The identification of a large number of mutations in the *FGFR2* gene has provided fascinating insight into the etiology of several skin and bone diseases, as well as some malignancies. The spectrum of disorders is underscored by a range of germline or somatic gain-of-function mutations or loss-of-function mutations in FGFR2. With regard to carcinogenesis, FGFR2 can have a dual role, acting either as an oncogene or as a tumor-suppressor gene. Observations in rodent models that oral administration of AZD2171 or Ki23057 inhibits *in vivo* proliferation of cancer cells with aberrant FGFR2 signaling activation provide a rationale for exploring the therapeutic potential of similar FGFR2 inhibitors in humans with malignancies associated with activating *FGFR2* mutations or *FGFR2* gene amplification. Nevertheless, FGFR2 inhibitors have the potential to disrupt several beneficial homeostatic processes, including cytoprotective mechanisms against environmental insults, such as UV irradiation, X-ray irradiation, chronic infection, and tobacco smoke. Consequently, any future pre-clinical studies on FGFR2 inhibitors will carefully need to consider the risk–benefit ratio, notwithstanding the considerable therapeutic modification these drugs might have on disease and tumor biology.

CONFLICT OF INTEREST

The author states no conflict of interest.

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